Irish Journal of Medical Science (1971 -) (2021) 190:981–986
https://doi.org/10.1007/s11845-020-02441-x

REVIEW ARTICLE

Resveratrol and cardiovascular system—the unfulfilled hopes

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Received: 3 November 2020 / Accepted: 16 November 2020 / Published online: 21 November 2020

Abstract

Introduction Resveratrol is a natural polyphenolic compound with a stilbene structure endowed with multiple health-promoting effects. Among phenolic compounds, resveratrol is assigned a leading role in the health-promoting effects of red wine.

Methods The aim of the study was to assess the effect of resveratrol on the cardiovascular system in the experimental and clinical studies conducted so far. Moreover, the paper discusses the results of the most recent meta-analyses assessing resveratrol's therapeutic effect on the cardiovascular system in humans.

Results In animal and preclinical studies, resveratrol has demonstrated a wide physiological and biochemical spectrum of activity, including antioxidant, anti-inflammatory, antiplatelet, and anticoagulant activities, which translated into its health-promoting effects on the cardiovascular system. The performed meta-analyses allow to confirm such an impact, however, after the assessment with the use of the SYRCLE's tool, these studies are burdened with a high risk of bias, and the results are not clearly presented.

Conclusion Despite numerous articles and clinical studies, the convincing beneficial mechanisms of resveratrol as well as its health-promoting effects in cardiovascular diseases have not been clearly confirmed in humans. Therefore, there is a need for further clinical studies, especially randomized, double-blind, placebo-controlled trials to objectively confirm the possible health-promoting effects of this substance and to determine both the efficacy and safety, and possible therapeutic potential.

Keywords Cardiovascular system · Cis-resveratrol · French paradox · Resveratrol · Trans-resveratrol · Wine

Introduction

Among phenolic compounds, resveratrol is assigned as a leading role in the health-promoting effects of red wine. Is this optimistic opinion confirmed by the documented real impact of this compound on the human body? How much wine does one need to drink each day for resveratrol to protect one's heart and cardiovascular system?

Resveratrol is a natural polyphenolic compound with a stilbene structure that occurs in two structurally distinct forms,

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namely, trans- and cis-resveratrol. Trans-resveratrol is the main active and stable form of resveratrol in grapes and grape juice, but many wines also contain significant amounts of cis-resveratrol [1, 2]. Resveratrol is produced by plants as a defense mechanism against various environmental threats, such as parasitic and fungal infections, ultraviolet radiation, chemical compounds, and mechanical damage [3]. It was first isolated in 1939 from the roots of white hellebore (*Veratrum grandiflorum*) [4], but the richest natural source of resveratrol is considered to be the Japanese knotweed root, which is mainly found in Japan and China. Large amounts of resveratrol were found in red wine, while lower concentrations in white wine, black grape varieties, peanuts, berries, apples, tomato peels, cocoa, and chocolate [5–7]. Concentrations in red wines vary from undetectable to about 14 mg/L, on average about 2 mg/L. In rosé and white wines, the concentrations of this compound are many times lower (even 3–10 times lower in white wines) [8]. The highest concentration of this stilbene is contained in grape skin and seeds, but its content is lower compared to other polyphenolic compounds contained in wine. Red wines with the highest content of resveratrol include Pinot noir, Merlot, Cabernet Sauvignon, Shiraz and the lesser-known strain of St. Laurent and Marzemino.

Resveratrol is absorbed in the jejunum and ileum. Human pharmacokinetic studies with trans-resveratrol have shown very low serum levels of unmetabolized resveratrol after oral administration. Resveratrol is well absorbed after oral administration, but its bioavailability is low and amounts to < 1% due to rapid metabolism in the intestine and liver, which affects the achieved plasma levels [3, 9]. The low bioavailability also results from the glycosylation of resveratrol, which increases the antioxidant capacity of this compound, but at the same time, increases its aqueous solubility, contributing to its increased excretion via urine [10].

On the other hand, high-fat foods delay the absorption of resveratrol. After a few hours, resveratrol metabolites are excreted from the bloodstream via urine and feces [2].

Health-promoting effect of resveratrol in experimental studies

In animal and preclinical studies, resveratrol has demonstrated a wide physiological and biochemical spectrum of activity, including antioxidant, anti-inflammatory, antiplatelet, and anticoagulant activities, which translated into its health-promoting effects on the cardiovascular system [11–13]. In experimental studies, resveratrol has shown, among others, that it inhibits the oxidation of cell membrane lipids, protecting low-density lipoproteins (LDL) from oxidation, and increasing the concentration of high-density lipoproteins (HDL). Resveratrol lowers lipid accumulation in human macrophage cultures by affecting cholesterol transport [14–16]. It also exhibits strong antioxidant properties, reducing the production of reactive oxygen species and scavenging free radicals [17–19]. It has an antithrombotic effect, inhibiting, among others, the synthesis of thromboxane and prostaglandins as well as the activity of platelets and pro-thrombotic mediators [20–22]. In experimental studies conducted in animal models, administration of grape juice or wine decreased the activity of pro-inflammatory cytokines and oxidative stress [23–25].

It has also been found that resveratrol dilates blood vessels in animals by stimulating the synthesis of nitric oxide, which plays a crucial role in protecting the arteries against the development of atherosclerosis [26–28]. In animal studies, the antidiabetic activity of resveratrol was demonstrated, among others, by protective effect on pancreatic cells [29, 30], decreased insulin resistance, and increased insulin content in pancreatic cells by regulating the activity of cellular mitochondria [31, 32].

The results of the conducted experimental studies confirm the occurrence of the above effects. The performed meta-analyses also allow to confirm such an impact, however, their authors emphasize that, after the assessment with the use of the SYRCLE's tool, these studies are burdened with a high risk of bias, and the results are not clearly presented [33].

Chen et al. emphasized that when interpreting animal experimental studies, apart from the result, also the limitations of these studies should be noticed. The occurrence of problems resulting from the low quality of the applied research method, the lack of sample size calculations, and above all, the high risk of bias is particularly important [34]. Summarizing the meta-analysis conducted, Toro et al. noted that most in vivo studies did not contain data that would allow excluding the risk of bias, in line with the SYRCLE's tool [35].

The analysis of the evaluation of the vascular endothelial function and the effect of resveratrol on arterial pressure by Akbari et al. showed that the supplementation of resveratrol significantly increases flow-mediated vasodilation (FMD) with no significant effect of resveratrol on systolic and diastolic pressure [36]. The authors conclude that additional prospective studies are needed to investigate the effects of resveratrol supplementation on endothelial function and blood pressure, and to perform long-term studies, using higher doses of resveratrol with longer durations.

Some authors publish completely contradictory results, the interpretation of which is difficult. Proper design of studies and standardization of their protocols will enable comparison of the studies with each other by means of meta-analyses. This requires the use of modern, repeatable methods as well as the publication of additional source data.

The anti-dementia and anti-aging effects of resveratrol

Recently, the anti-dementia and anti-aging effects of resveratrol have aroused strong interest among researchers. It has been

shown, among others that long-term limitation of caloric intake in the diet (below 30–50% of the demand) slows down the aging process and thus prolongs the life of many organisms, including rodents and primates [37, 38]. This effect does not occur when genes encoding Sir proteins (silent information regulator, sirtuins) are damaged, but it is enhanced in the case of increased expression of these genes [39]. In vitro and in vivo studies have shown that some red wine polyphenols extend the lifespan and delay the cell aging mechanism by activating sirtuins. Resveratrol is particularly active, as it enzymatically increases the expression of human SIRT1 in vitro by about 13-fold, regulating the lifespan by a similar mechanism as caloric restriction [40, 41]. Resveratrol also inhibits the formation of fat cells and reduces the amount of adipose tissue, which is important in the pathogenesis of cardiovascular and neurodegenerative diseases [42–44]. The conducted studies also confirmed the protective and therapeutic effects of resveratrol in the nervous system, especially in Alzheimer's disease [45, 46]. It has been found in animal models that resveratrol affects the hippocampal cells of the brain, protecting them against the toxic effects of β-amyloid, which is expected to slow down the development of this disease [47]. Moreover, it has also been reported that resveratrol may reduce the predisposition to depressive states, reduce the symptoms of dementia, and improve learning and spatial memory by improving cerebral vascular flow [48–50]. Therefore, the results of the conducted studies give hope that resveratrol could be used to develop new drugs that would inhibit the aging process, preserve youth, health, and vitality for longer [51, 52].

Clinical studies of resveratrol

It is important to consider how the diverse potential of resveratrol translates into its health-promoting effects in clinical studies, and what is the benefit for the heart and vessels of consuming one or two glasses of red wine and resveratrol it contains? In order to use strong arguments in response, data from studies with the highest impact, i.e., resulting from meta-analyses of randomized clinical studies, were taken into account. These publications are few and between, and not always consistent, but they shed light on the clinical health-promoting effects of resveratrol.

Resveratrol has been shown to be effective in humans with hypertension, but mostly when using high doses above 300 mg/day [50] or 150 mg/day [53, 54]. In humans with obesity or overweight, it allowed for weight loss [55, 56]. In humans suffering from diabetes, a reduction in fasting glucose levels and glycosylated hemoglobin (HbA1C), and an increase in insulin sensitivity were observed at doses over 100 mg/day [57]. The results of clinical studies concerning the resveratrol's positive effect on the lipid metabolism seem to be rather weak, as no significant reduction in LDL cholesterol was observed [58]. Moreover, in one of the randomized studies using a dose of 150 mg/day or 1000 mg/day for 16 weeks in 74 humans with metabolic syndrome, a significant increase in both LDL and total cholesterol levels was observed [59]. The results of meta-analyses of randomized clinical studies on the resveratrol`s anti-inflammatory activity are also quite inconsistent, as both a decrease in CRP and IL-6 levels was observed [60, 61] or no changes in CRP levels were noted [62]. The results of clinical studies assessing the beneficial effect of resveratrol, both in humans with chronic coronary disease [63, 64] and left ventricular dysfunction after myocardial infarction [65] were also not convincing and required further well-designed studies.

Wine, resveratrol, and the French paradox

A scientific promoter of the French paradox, Prof. Serge Renaud, formulated a theory of lower incidence and mortality due to ischemic heart disease among the inhabitants of the Bordeaux region, despite high levels of dietary saturated fat and cigarette smoking, which he justified with consumption of red wine with meals (customary in this part of Europe) and the polyphenols contained in it [66]. Over the years, this beneficial role has been increasingly attributed to resveratrol.

It should be remembered that the current recommendations regarding the daily health-promoting dose of this compound are based mainly on arithmetical animal-to-human dosage conversion. Based on these calculations, it was concluded that a dose of 1 g/day resveratrol could be both an effective and a safe dose. In the randomized clinical studies mentioned above, daily doses of resveratrol ranged from 100 mg to 1 g.

While critically assessing the role of resveratrol in the French paradox, attention should be paid not only to the low bioavailability of this compound, resulting mainly from the rapid elimination of resveratrol from the body, but also to the fact that the transfer of results from in vitro studies and animal models to humans have not brought the expected results so far. The concentrations used in these studies are much higher than can be obtained in the human body with the habitual consumption of red wine. It is possible to achieve higher concentrations of resveratrol in human plasma, but only by using additional resveratrol-enriched supplements, even at the promoted dose of 1 g/day. Various reports of mediocre or no scientific value try to convince the consumer that the resveratrol contained in the supplements allows to achieve an health-promoting effect and protect the heart from a myocardial infarction.

The concentration of resveratrol in wine varies depending on the type of strain, vineyard, microclimate, and year. Different wine-making processes, including temperature, obtained pH, and sulfur dioxide content in wine, also influence the concentration of resveratrol. However, all these factors

make it difficult to precisely determine the content of this substance contained in natural products [67, 68].

This raises the question: what dose of resveratrol should be considered clinically effective and safe at the same time? In clinical studies with volunteers, the high doses of 2–5 g resveratrol/day were safe, but often caused gastrointestinal discomfort. Much lower dosages of 100–300 mg/day, also allowed to achieve a therapeutic effect in randomized clinical studies, which this gave rise to another scientific dilemma: what doses of resveratrol should be used in specific diseases without concerns about the safety of the drug [69, 70]? Considering the resveratrol contained in red wine, the question is, how much would one need to drink per day to reach a dose of at least 100 mg resveratrol/day?

The average concentration of resveratrol in red wines ranges from 0.36 to 2.0 mg/L [71]; in white wines, it is much lower from 0 to 1.1 mg/L [72]; and in rosé wines, it is approximately 0.3 mg/L [73]. According to 2014 data from the Global Agricultural Information Network, an average French drinks about 44 L of wine a year, of which 75% are red wines and 25% white wines [74]. Assuming that red wine contains about 2 mg/L resveratrol, a consumption of 44 L of wine is equals 70 mg resveratrol/year or 0.2 mg/day, which is 500 times less than the dose of 100 mg/day. This means that one would need to drink 50 L of wine or eat 250 kg of apples daily to achieve the beneficial health effects associated with resveratrol. Even including resveratrol contained in other natural products, this calculation clearly proves that consuming resveratrol contained in natural products is not enough to explain the mechanism of the French paradox. Especially since one cannot be sure whether higher doses would be safe for the heart.

Studies conducted on rats show that even doses of above 25 mg/day increased the area of myocardial infarction and cardiomyocyte apoptosis [75]. One more important question should be asked—is resveratrol supplementation always safe for health? Bearing in mind that the exact molecular mechanism responsible for the pleiotropic beneficial effects of this compound remains unclear and controversial, the safety of resveratrol-enriched supplements is also questioned. Resveratrol can inhibit platelet aggregation in humans in vitro, therefore, theoretically, high resveratrol intake may increase the risk of bleeding in people taking anticoagulants, antiplatelet drugs, and non-steroidal anti-inflammatory drugs [22].

Conclusion

More than 80 years have passed since the first isolation of resveratrol in 1939 from the roots of the white hellebore. More than 20,000 articles related to resveratrol have been published and more than 130 clinical studies have been conducted, however, the convincing beneficial mechanisms of resveratrol as well as its health-promoting effects in cardiovascular diseases have not been clearly confirmed in humans [76]. Therefore, there is a need for further clinical studies, especially randomized, double-blind, and placebo-controlled trials to objectively confirm the possible health-promoting effects of this substance and to determine both the efficacy and safety, and possible therapeutic potential, both in natural products, including wine and in resveratrol-enriched supplements. Therefore, while waiting for convincing scientific data, there is nothing left but to consume red wine with the optimistic conviction that resveratrol contained in this drink has a positive effect on health.

Authors' contributions MC—conception and design of the article, interpreting the relevant literature, drafting of manuscript;
DR—conception and design of the article, interpreting the relevant literature, drafting of manuscript;
ŁW—interpreting the relevant literature, drafting of manuscript;
JB—interpreting the relevant literature, drafting of manuscript;
SS—conception and design of the article, interpreting the relevant literature;
RB—literature review, drafting of manuscript;
AS—literature review, critical revision;
GG—critical revision, proofreading of the version for publication.
All authors read and approved the final manuscript.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

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